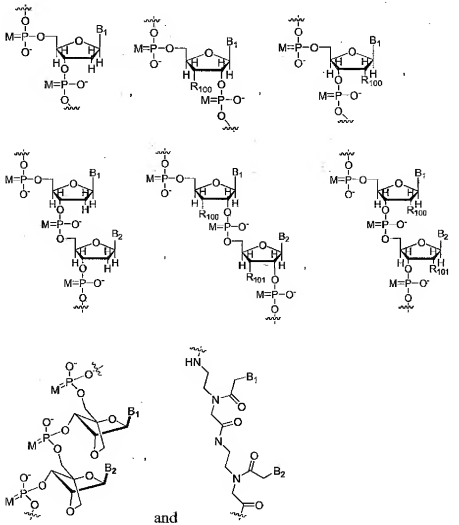
AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims:

1. (Cancelled)

2. (Currently Amended) The prodrug of claim 27, wherein the oligonucleotide comprises a nucleotide that is selected from the group consisting of



and

wherein

M is O or S;

B_1 and B_2 are independently selected from the group consisting of A (adenine), G (guanine), C (cytosine), T (thymine), U (uracil) and modified bases;

R_{100} and R_{101} are independently selected from the group consisting of H, OR' where R' is H, a $C_{1\text{-}6}$ alkyl, substituted alkyls, nitro, halo and aryl.

3. (Cancelled)

4. (Previously Presented) The prodrug of claim 2, wherein M is S.

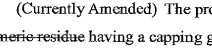
5. (Previously Presented) The prodrug of claim 27, wherein the oligonucleotide residue is a phosphorothioate oligonucleotide residue.

6. (Previously Presented) The prodrug of claim 27, wherein said oligonucleotide residue is an antisense oligonucleotide residue or oligodeoxynucleotide residue.

7. (Currently Amended) The prodrug of claim 6, wherein said antisense oligonucleotide residue or oligodeoxynucleotide residue is selected from the group consisting of [[,]] oligonucleotides and oligodeoxynucleotides with phosphorodiester backbones or phosphorothioate backbones, LNA, PNA, tricyclo-DNA, decoy ODN, ribozymes, spiegelmers, and CpG oligomers.

8. (Previously Presented) The prodrug of claim 6, wherein said antisense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, wherein n of SEQ ID NO: 4 is any nucleotide.

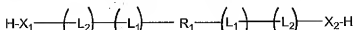
9. (Currently Amended) The prodrug of claim 27, wherein R_1 is a polyalkylene oxide ~~polymeric residue~~ having a capping group A, selected from the group consisting of OH, NH_2, SH, CO_2H, $C_{1\text{-}6}$ alkyls, and



(II)

wherein X_2 is a single stranded or double stranded oligonucleotide residues, wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides.

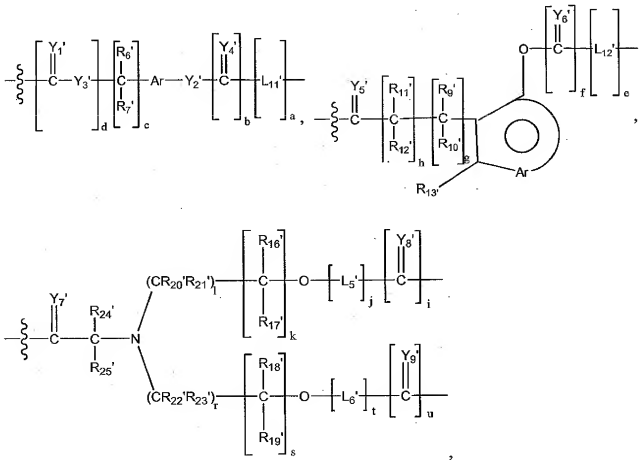
10. (Currently Amended) A prodrug of claim 9, selected from the group consisting of:

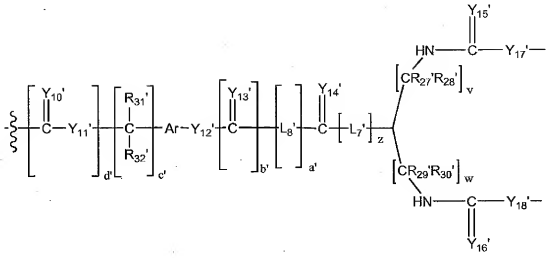


wherein ~~each~~ X_2 is ~~independently~~ a 3' oligonucleotide or 5' oligonucleotide.

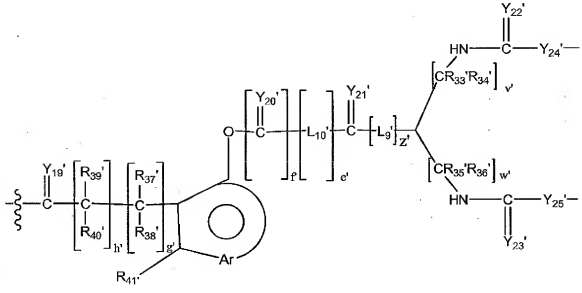
11. (Cancelled)

12. (Currently Amended) The prodrug of claim 27, wherein L_1 is selected from the group consisting of:





and



wherein,

$Y_{1'}$-$Y_{25'}$ are independently selected from the group consisting of O, S or NR_9;

$R_{6'-7'}$, $R_{9'-13'}$, $R_{16'-25'}$, R_9 and $R_{27'-41'}$ are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, ~~C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls,~~ aryls, ~~substituted aryls, aralkyls,~~ C_{1-6} heteroalkyls, ~~substituted C_{1-6} heteroalkyls,~~ C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy;

$L_{5'-12'}$ are independently selected bifunctional spacers;

Ar is a moiety which forms a multi-substituted aromatic hydrocarbon or a multi-substituted heterocyclic group;

c, h, k, l, r, s, v, w, v', w', c', and h' are independently selected positive integers;

a, e, g, j, t, z, a', z', e' and g' are independently either zero or a positive integer; and b, d, f, i, u, b', d' and f' are independently zero or one.

13. (Cancelled)

14. (Currently Amended) The prodrug of claim 27, wherein R_1 is a ~~polyalylene~~ polyethylene glycol.

15. (Currently Amended) The prodrug of claim 27, wherein R_1 is selected from the group consisting of:

J- O-$(CH_2CH_2O)_{n'}$-

J-O-$(CH_2CH_2O)_{n'}$-$CH_2C(O)$-O-,

J-O-$(CH_2CH_2O)_{n'}$-CH_2CH_2 NR_{48}-,

J-O-$(CH_2CH_2O)_{n'}$-CH_2CH_2 SH,

-O-C(O)CH_2-O-$(CH_2CH_2O)_{n'}$-$CH_2C(O)$-O-,
-$NR_{48}CH_2CH_2$-O-$(CH_2CH_2O)_{n'}$-CH_2CH_2 NR_{48}-,
-SHCH_2CH_2-O-$(CH_2CH_2O)_{n'}$-CH_2CH_2 SH-,

wherein

n' is the degree of polymerization;

R_{48} is selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, ~~C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls,~~ aryls, ~~substituted aryls, aralkyls,~~ C_{1-6} heteroalkyls, ~~substituted C_{1-6} heteroalkyls,~~ C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy; and

J is a capping group.

16. (Previously Presented) The prodrug of claim 27, wherein R_1 comprises

- O-$(CH_2CH_2O)_x$ –

wherein x is a positive integer selected so that the weight average molecular weight is at least about 2,000 Da to about 136,000 Da.

17. (Previously Presented) The prodrug of claim 27, wherein R_1 has a weight average

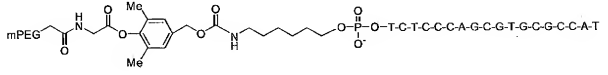
molecular weight of from about 3,000 Da to about 100,000 Da.

18. (Previously Presented) The prodrug of claim 27, wherein R_1 has a weight average molecular weight of from about 5,000 Da to about 40,000 Da.

19. (Previously Presented) The prodrug of claim 8, wherein said antisense oligonucleotide is oblimersen (SEQ ID NO: 1).

20. (Cancelled)

21. (Currently Amended) The prodrug of claim 27 selected from the group consisting of:



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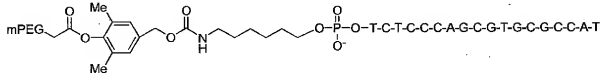
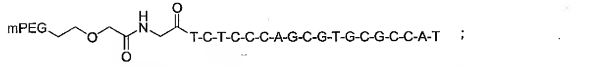


;

and



;

wherein all of which comprise an oligonucleotide of SEQ ID NO: 1.

22. (Withdrawn/Currently Amended) A method of making a prodrug comprising:

reacting a compound of the formula:

R_1-L_1-leaving group

with a compound of the formula:

H-L_2-X_1

under conditions sufficient to form a prodrug of the formula

X_1-L_2-L_1-R_1 ~~R_1-L_1-L_2-X_1~~ ,

wherein:

R_1 is a polyalkylene oxide ~~polymer residue~~;

L_1 is a releasable linking moiety;

L_2 is a bifunctional spacing group comprising from about 2 to about 10 carbon atoms; and

X_1 is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides,

wherein L_2 is selected from the group consisting of

$-(CR_{50'}R_{51'})_{q'}Q'-$,

$-(CR_{52'}R_{53'})_{r'}O(CR_{50'}R_{51'})_{q'}Q'-$,

$-(CR_{52'}R_{53'})_{r'}(OCH_2CH_2)Q'-$,and

$-(CH_2)_{r'}-S-S-(CH_2)_{q'}Q'-$,

wherein

Q' is O, S or NH;

$R_{50'-53'}$ are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, aryls, C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy; and

q' and r' are each a positive integer.

23-26. (Cancelled)

27. (Currently Amended) An oligonucleotide prodrug of the formula ~~(I)~~:

X_1-$(L_2)_n$-$(L_1)_o$-R_1 ~~R_1-$(L_1)_o$-$(L_2)_n$-X_1 (I)~~

wherein:

R_1 is a polyalkylene oxide ~~polymer residue~~;

L_1 a releasable linking moiety;

L_2 is a selected bifunctional spacing group comprising from about 2 to about 10 carbon atoms;

X_1 is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides;

n, and o are independently a positive integer; and

provided that (o + n) ≥ 2,

wherein

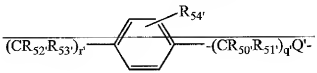
L_2 is selected from the group consisting of:

$-(CR_{50'}R_{51'})_{q'}Q'-$,

$-(CR_{52'}R_{53'})_{r'}O(CR_{50'}R_{51'})_{q'}Q'-$,

$-(CR_{52'}R_{53'})_{r'}(OCH_2CH_2)Q'-$,

~~$-(CR_{52'}R_{53'})_{r'}C(O)NH(CR_{50'}R_{51'})_{q'}Q'-$,~~



and

~~$-(CH_2)-S-S-(CH_2)_{q'}Q'-$~~

$-(CH_2)_{r'}-S-S-(CH_2)_{q'}Q'-$,

wherein

Q' is O, S or NH;

$R_{50'-53'}$ are independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{3-8} cycloalkyls, ~~C_{1-6} substituted alkyls, C_{2-8} substituted cyloalkyls,~~ aryls ~~substituted aryls, aralkyls,~~ C_{1-6} heteroalkyls, ~~substituted C_{1-6} heteroalkyls,~~ C_{1-6} alkoxy, phenoxy and C_{1-6} heteroalkoxy;

~~$R_{54'}$ is independently selected from the group consisting of hydrogen, C_{1-6} alkyls, C_{3-12} branched alkyls, C_{2-8} cycloalkyls, C_{1-6} substituted alkyls, C_{3-8} substituted cyloalkyls, aryls substituted aryls, aralkyls, C_{1-6} heteroalkyls, substituted C_{1-6} heteroalkyls, C_{1-6} alkoxy, phenoxy, C_{1-6} heteroalkoxy, NO_2, haloalkyl and halogen;~~ and

q' and r' are each a positive integer.

28. (New) An oligonucleotide prodrug prepared by a process comprising:

reacting a compound of the formula:

R_1-L_1-leaving group

with a compound of the formula:

$H\text{-}L_2\text{-}X_1$

under conditions sufficient to form a prodrug of the formula

$X_1\text{-}L_2\text{-}L_1\text{-}R_1$,

wherein

R_1 is a polyalkylene oxide;

L_1 is a releasable linking moiety;

L_2 is a bifunctional spacing group comprising from about 2 to about 10 carbon atoms; and

X_1 is a single or double stranded oligonucleotide residue wherein the oligonucleotide ranges in size from 10 to 1,000 nucleotides,

wherein L_2 is selected from the group consisting of:

$-(CR_{50'}R_{51'})_{q'}Q'-$,

$-(CR_{52'}R_{53'})_{r'}O(CR_{50'}R_{51'})_{q'}Q'-$,

$-(CR_{52'}R_{53'})_{r'}(OCH_2CH_2)Q'-$, and

$-(CH_2)_{r'}\text{-}S\text{-}S\text{-}(CH_2)_{q'}Q'-$,

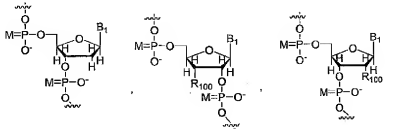
wherein

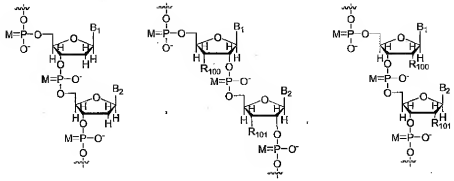
Q' is O, S or NH;

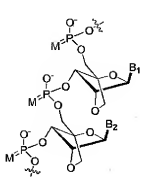
$R_{50'\text{-}53'}$ are independently selected from the group consisting of hydrogen, $C_{1\text{-}6}$ alkyls, $C_{3\text{-}12}$ branched alkyls, $C_{3\text{-}8}$ cycloalkyls, aryls, $C_{1\text{-}6}$ heteroalkyls, $C_{1\text{-}6}$ alkoxy, phenoxy and $C_{1\text{-}6}$ heteroalkoxy; and

q' and r' are each a positive integer.

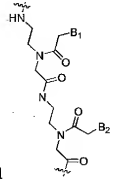
29. (New) The prodrug of claim 28, wherein X_1 comprises a nucleotide selected from the group consisting of







and



wherein

M is O or S;

B_1 and B_2 are independently selected from the group consisting of A (adenine), G (guanine), C (cytosine), T (thymine), U (uracil) and modified bases thereof;

R_{100} and R_{101} are independently selected from the group consisting of H, OR' where R' is H, a $C_{1\text{-}6}$ alkyl, substituted alkyls, nitro, halo and aryl.

30. (New) The prodrug of claim 28, wherein X_1 is selected from the group consisting of oligonucleotides with phosphorodiester backbones or phosphorothioate backbones, LNA, PNA, tricyclo-DNA, decoy ODN, ribozymes, spiegelmers, and CpG oligomers.

31. (New) The prodrug of claim 28, wherein X_1 includes a phosphorothioate backbone.

32. (New) The prodrug of claim 28, wherein X_1 is an antisense oligonucleotide.

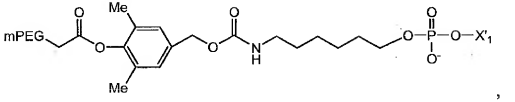
33. (New) The prodrug of claim 32, wherein the antisense oligonucleotide has a sequence selected from the group consisting of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, and SEQ ID NO: 4, wherein n of SEQ ID NO: 4 is any nucleotide.

34. (New) The prodrug of claim 28, wherein R_1 is a polyalkylene glycol.

35. (New) The prodrug of claim 28, wherein R_1 has a weight average molecular weight of from about 3,000 Da to about 100,000 Da.

36. (New) The prodrug of claim 34, wherein R_1 has a weight average molecular weight of from about 5,000 Da to about 40,000 Da.

37. (New) The prodrug of claim 28 selected from the group consisting of



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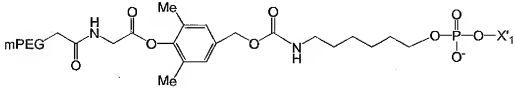

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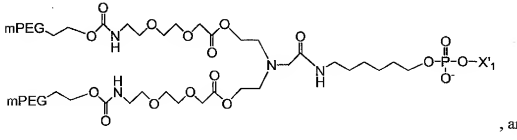
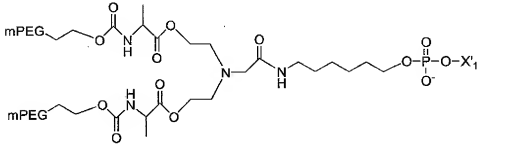


, and



wherein

represents an oligonucleotide and point of terminal phosphate modification; and

mPEG is $CH_3O(CH_2CH_2O)_X$-, wherein x is a positive integer selected from about 10 to about 2300.